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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,936	09/23/2003	Michele Sanicola-Nadel	13751-045003	3298

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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
HARRIS, ALANA M	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,936	SANICOLA-NADEL ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3-5* is/are allowed.

6)☒ Claim(s) *1,2 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 1-4, SEQ ID NO: 21) in the reply filed on June 26, 2006 is acknowledged. The traversal is on the ground(s) that SEQ ID NO: 17 and SEQ ID NO: 21 are highly related and would pose no undue burden to the Examiner to examine both groups comprising SEQ ID NO: 17 and SEQ ID NO: 21. This argument has been found persuasive and the requirement is withdrawn.

2. Claims 1-10 are pending.

Claim 2 has been amended.

Claims 5-10 have been added.

Claims 1-10 are examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2 and 6-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim language

reads on isolated polypeptides comprising amino acid sequences at least 80%-95% identical to amino acid sequences identified as SEQ ID NO: 17 and SEQ ID NO: 21. Accordingly, one of skill in the art cannot ready envisage the identity of the members of the genera. The written description in this case only sets forth Ret ligand (RetL) polypeptides, SEQ ID NO: 17 (murine RetL3 aa) and SEQ ID NO: 21 (human retL3 aa) listed in section 0035 of page 7. Applicants are not in possession of all proteins that have reduced sequence homology to wild type proteins, SEQ ID NO: 17 and SEQ ID NO: 21. The written description in this case only sets forth Ret ligands as listed in claims 3-5.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Applicants are not required to disclose every species encompassed by a genus. For example as indicated in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An

adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Applicants broadly claim anti-Ret antibodies capable of blocking binding of a Ret ligand polypeptide to a Ret polypeptide. However, Applicants are not entitled, nor is the specification enabled for the use of all RetL polypeptides capable of playing a role in the Ret signaling pathway including stimulating renal and/or neuronal cell growth or survival in disease situations. Applicants are only in possession of 2 species, which are not defined by structure. Applicants are not permitted to claim all the mutated and variant polypeptides that are encompassed by the claim language of the claims, hence not entitled to the wide breadth of the claims at issue. As Applicants' claims are written the claimed polypeptides with reduced sequence homology encompass variants. There is no description and no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others are excluded and missing from the disclosure, as well as features of the antigen.

Furthermore, with the exception of SEQ ID NOs: 17 and 21, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*,

25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

5. Claim 1, 2 and 6-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The genus claimed in the independent claims encompasses variant Ret ligand polypeptides, which share 80%-95% sequence identity to SEQ ID NO: 17 and SEQ ID NO: 21. These variant molecules have numerous differences in amino acid sequences, including numerous differences in linear and conformational epitopes.

However, the present specification fails to provide sufficient disclosure of such variant Ret ligand polypeptides, which maintain the structural and functional properties of the Ret polypeptide set forth in murine RetL3 (SEQ ID NO: 17) and human RetL3 (SEQ ID NO: 21). The specification does not provide sufficient guidance as to which of the amino acids may be changed while Ret structural or functional activity and specificity is retained.

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a

monoclonal antibody (see entire document). For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

Because of this lack of guidance, the extended experimentation that would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et al.; in The Protein Folding Problem and Tertiary Structure Prediction,1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to arrive at the other Ret polypeptides encompassed by the claimed invention.

The scope of the claimed Ret polypeptides is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of Ret polypeptides broadly encompassed by the claimed invention. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's or peptide's amino acid sequence, and, in turn, nucleic acid sequence, and still retain similar biological activity or structural specificity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a limited number of proteins/nucleic acids and in

turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Thus, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed Ret polypeptides in a manner reasonably correlated with the scope of the claims broadly including a broad number of structural changes encompassed by amino acid substitution variants of the Ret ligand polypeptides. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the Ret encoding nucleic acids and amino acids and still maintain biological activity or structural specificity of Ret ligands is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 2 and 6 do not further limit from claim 1.

Allowable Subject Matter

8. Claims 3-5 are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571) 272-0831. The Examiner works a flexible schedule, however she can normally be reached between the hours of 7:30 am to 6:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
05 September 2006